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## SLEEP AND THE FUNCTIONAL CONNECTOME

Dante Picchioni, PhD<sup>1</sup>, Jeff H. Duyn, PhD<sup>2</sup>, and Silvina G. Horovitz, PhD<sup>3</sup>

<sup>1</sup>Department of Behavioral Biology, Walter Reed Army Institute of Research, Silver Spring, MD, USA

<sup>2</sup>Advanced MRI, LFMI, NINDS - National Institutes of Health, Bethesda, MD, 20892, USA

<sup>3</sup>Human Motor Control Section, MNB, NINDS - National Institutes of Health, Bethesda, MD, 20892, USA

### Abstract

Sleep and the functional connectome are research areas with considerable overlap. Neuroimaging studies of sleep based on EEG-PET and EEG-fMRI are revealing the brain networks that support sleep, as well as networks that may support the roles and processes attributed to sleep. For example, phenomena such as arousal and consciousness are substantially modulated during sleep, and one would expect this modulation to be reflected in altered network activity. In addition, recent work suggests that sleep also has a number of adaptive functions that support waking activity. Thus the study of sleep may elucidate the circuits and processes that support waking function and complement information obtained from fMRI during waking conditions. In this review, we will discuss examples of this for memory, arousal, and consciousness after providing a brief background on sleep and on studying it with fMRI.

### Keywords

Sleep; connectivity; memory; arousal; consciousness

## INTRODUCTION

A major goal of recent efforts to map the human functional connectome (Biswal et al., 2010) is to chart circuits that underlie the brain's functions. These efforts have been facilitated by the use of functional MRI (fMRI), which allows the study of large-scale circuits with full-brain coverage, provides a spatial resolution of a few millimeters, and provides a temporal resolution of a few seconds. Many of the recent fMRI-based studies performed in the context of the functional connectome have relied on the notion that human subjects not involved with any particular task or behavior display a remarkable amount of brain activity that involves most brain regions (Biswal et al., 2010). Although the function of this activity is still incompletely understood, it appears to reflect important aspects of the brain's

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Corresponding author: Silvina G. Horovitz, Ph.D., Human Motor Control Section, Medical Neurology Branch, NINDS, NIH, 10 Center Drive, Bldg 10/7D37, Bethesda, MD, 20892 Phone: + 1 301.435.2163 fax: + 1 301.480.228, silvina.horovitz@nih.gov.

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circuitry. Thus fMRI during rest may provide information that is complementary to information from studies performed during specific tasks or behaviors.

Interestingly, much of this spontaneous fMRI activity continues during conditions (e.g., anesthesia and sleep) when interaction with the environment and voluntary mentation are reduced (Boveroux et al., 2010; Fukunaga et al., 2006; Vincent et al., 2007). Understanding the nature of the spontaneous fMRI activity is complicated by the fact that both sleep and spontaneous fMRI activity are far from well understood. Nevertheless, because cortical circuits that differ from wakefulness to sleep and between substates of sleep have been identified with both PET and fMRI, the study of fMRI activity during sleep may allow the identification of circuits that support the unique functions and behaviors that are associated with sleep and thus improve our understanding of sleep. These circuits can be divided into those that regulate sleep in a bottom-up manner versus those that regulate sleep in a top-down manner. The former could be said to regulate sleep behavior in general and require nuclei in the brainstem/hypothalamus and basal forebrain that project to the cortex, whereas the latter may be more important for the use-dependent functions of sleep that originate in the cortex (Krueger et al., 2008). fMRI may not be optimal to map circuits that involve subcortical nuclei, but it may be well-suited to measure cortical circuits associated with use-dependent activity during wakefulness.

Use-dependent theories of sleep function as well as other theoretical and methodological expositions on the functions of sleep are often limited to mechanistic functions. This means that they do not necessarily relate brain activity during sleep to a specific feature of cognition that changes during a subsequent period of wakefulness and that is evolutionarily adaptive. Recent work suggests that sleep indeed has a number of adaptive functions that support waking activity in this way (e.g., memory consolidation; (Walker and Stickgold, 2004), emotion regulation (Stickgold, 2002; Walker, 2009)). Thus the study of sleep may elucidate the circuits and processes that support waking function and complement information obtained from fMRI during waking conditions. In this review, we will discuss examples of this for memory, arousal, and consciousness after providing a brief background on sleep and on studying it with fMRI. Although other methods can be used to measure connectivity during sleep (e.g., magnetoencephalography), we will focus on fMRI to provide a more concise and clearly circumscribed review.

## BRAIN CIRCUITS THAT SUPPORT SLEEP

The identification of different brain states is accomplished with polysomnography, which is the combined use electroencephalography (EEG), electro-oculography, and electromyography. The different brain states are classified as wakefulness, REM sleep, and non-REM sleep, and non-REM sleep is further divided according to depth of sleep (i.e., stages N1–N3 (AASM, 2007) or stages S1–S4 (Rechtschaffen and Kales, 1968)). Non-REM sleep is also divided in light sleep (including N1 (or S1)), N2 (or S2), and deep sleep, also called slow wave sleep (SWS) and includes N3 (and S3–S4) (see Table). Sleep onset is thought to result from an increased sleep drive mediated by homeostatic and circadian factors. The homeostatic factors are reflected in ATP depletion and adenosine accumulation, which eventually lead to reduced acetylcholine release, for example, by the main wake-promoting system known as the ascending reticular activating system (ARAS) (Moruzzi and Magoun, 1949). Cholinergic activity in this system is also responsible for REM sleep. Animal studies have shown that sleep control may also be effectuated by inhibitory inputs to wake-promoting systems such as the ARAS by the ventro-lateral preoptic area (McGinty and Szymusiak, 2000; Saper et al., 2001).

Another important region involved in the modulatory control of brain activity during sleep is the thalamus, which serves as the gatekeeper for sensory input to the cortex and which has extensive, bidirectional connections with the cortex through thalamocortical loops. The thalamus contains nonspecific nuclei that relay signals from the ARAS to the entire neocortex (see Figure). The thalamus is thus well-suited to mediate neocortical arousal throughout the sleep-wake cycle. In fact, many studies have demonstrated thalamic involvement in the electrophysiological manifestations of sleep including K-complexes, spindles, and slow oscillations (see review by (Llinas and Steriade, 2006)).

During sleep, the brain remains metabolically and electrically active. In part, this activity serves to regulate sleep. This includes circadian cycling from wake to sleep and ultradian cycling between rapid eye movement (REM) and non-REM sleep. Importantly, we know of several brain mechanisms that explain the relatively rapid transitions (seconds to minutes) that occur between these stages. However, when considering these mechanisms, it is important to bear in mind that other unknown repetitive patterns may exist during sleep beyond the traditional REM/non-REM patterns.

A primary mechanism that supports sleep regulation is neuromodulation by regions such as the hypothalamus (e.g., the ventro-lateral preoptic nucleus), pons, and basal forebrain. These brain regions are involved in modulating excitability and activity in downstream regions through neurotransmitters such as GABA, acetylcholine, hypocretin/orexin, norepinephrine, and serotonin. Such neurotransmitters can be released by modulatory neurons and remotely alter the configuration of and activity in downstream micro- and macro-circuits (Marder, 2012). The various basal forebrain and brainstem nuclei that have been identified to play a role in the regulation of sleep interact in a complicated fashion and generally involve multiple neurotransmitters (Saper et al., 2005). Distinct mechanisms have been proposed that facilitate the transitions between wake and non-REM sleep and between non-REM and REM sleep (McCarley and Hobson, 1975; Saper et al., 2010; Saper et al., 2005). Generally, the transitions between wakefulness and sleep are controlled via hypothalamic modulation of brainstem regions, whereas ultradian cycles are controlled via interaction of brainstem reticular regions.

In terms of the mnemonic functions of sleep, some have suggested that different sleep stages support different memory systems (Plihal and Born, 1997; Smith, 2001), whereas others have suggested that the cycling itself is important so that different sleep stages support different memory processes (Giuditta et al., 1995). For example, non-REM might weaken superfluous memories through global synaptic downscaling (Tononi and Cirelli, 2006), and REM sleep may strengthen the remaining memories through ponto-geniculo-occipital (PGO) wave-based reactivation of allocortical and neocortical regions (Mavanji and Datta, 2003). In addition, sleep features other than PGO- waves and slow waves may be relevant for memory consolidation (e.g., sleep spindles and hippocampal sharp-wave ripples).

## EEG-FMRI OF SLEEP

The gold standard for defining sleep is a set of behavioral characteristics that include an increased arousal threshold (Campbell and Tobler, 1984; Moruzzi, 1969; Piéron, 1913). However, in practice, the EEG has become a widely accepted surrogate for the behavioral definitions because of the strong correlation between EEG slow waves and arousal threshold (e.g., (Blake and Gerard, 1937)). Therefore, the study of network activity specific to sleep is approached with the combined use of electroencephalography (EEG) scalp recordings and neuroimaging methods such as Positron Emission Tomography (PET) and fMRI (for review see (Duyn, 2012)). Conjoint analysis of EEG and positron emission tomography (PET) or fMRI overcomes some of the drawbacks that each method has when used in isolation. For

example, many sleep-specific neuro-electrical phenomena such as sleep, K-complexes, and slow waves can be detected easily and with temporal precision (ms) with EEG. Currently, this is not possible with fMRI alone. On the other hand, a drawback of EEG is its poor (cm) spatial resolution and the fact that it only captures a small fraction of the broad repertoire of electrical activity generated in the brain. For example, EEG is relatively sensitive to superficial sources (close to the scalp) of synchronized electrical activity in large neuronal ensembles with isotropically organized dendrites but much less so for other types of sources. FMRI, on the other hand, has better spatial resolution (mm) and can detect deep sources, but it has a poor temporal resolution (seconds) and only indirectly detects neuronal activity through blood flow and BOLD effects. Like EEG, fMRI does not detect all types of activity and is likely not equally sensitive in all brain regions (Logothetis, 2008). In summary, combined EEG-fMRI may allow the characterization of sleep-specific brain activity with better sensitivity and precision than each modality alone.

Conjoint analysis of EEG-fMRI data can proceed in various ways (Duyn, 2012). In order to study differences in brain activity between the different stages of sleep, EEG can be used simply to detect or stage sleep, after which, fMRI can be analyzed for correlational structure or fluctuation level in a stage-specific manner (e.g., (Horovitz et al., 2009; Horovitz et al., 2008; Spoormaker et al., 2010)). Alternatively, fMRI correlates of specific EEG features can be analyzed. For this purpose, power in specific EEG frequency bands or specific microarchitecture features such as K-complexes or spindles can be extracted and regressed against the fMRI signal (e.g., (Schabus et al., 2007)).

In general, it has been found that the correlation between EEG and fMRI signals is generally low ( $<0.5$ ), and this may not be surprising given the two modalities measure different aspects of neuronal activity. Interpretation of EEG-fMRI correlations should be done with caution and should take into consideration the fact that the underlying signals originate from the simultaneous activity of large neuronal ensembles and have inadequate sensitivity and temporal and spatial resolution to capture neuronal spiking in local circuits. In particular, when applied to the study of sleep, connectivity measures derived from EEG-fMRI may emphasize the relatively slow modulatory effects of neuronal activity and excitability that are prevalent in sleep (Olbrich et al., 2011). Another limitation that applies to functional connectivity studies in general is the risk of false negatives, i.e. the absence of signal correlation does not negate the presence of a network connection because it may simply be caused by down regulation of activity.

## FMRI CHANGES WITH SLEEP

Although the application of fMRI to sleep is a relatively novel research area that is still in its infancy, initial studies are providing a wealth of information about sleep networks and their various functions that support waking behavior. A brief overview of these findings will be presented in this section, whereas specific examples of network functions that undergo changes during sleep, namely memory, consciousness, and arousal, are discussed in following sections (see Figure).

Most fMRI studies have focused on non-REM sleep and a general finding has been a preservation of fMRI signal fluctuations and correlations across the brain (e.g. (Horovitz et al., 2008)). Earlier PET work found a reduction of CBF with the deepening of sleep in most brain areas (Braun et al., 1997; Maquet, 2000), with the exception of unimodal sensory areas where rCBF was preserved. The reticular formation and its dorsal and ventral projections have reduced rCBF during sleep compared to wake (Braun et al., 1997). Within these projections, the hypothalamus and the heteromodal cortices have a strong functional connectivity during sleep and an absence of this connectivity during wakefulness

(Kaufmann et al., 2006). These apparent discrepancies between modalities may result from the fact that rCBF (measured with PET) and its fluctuation (measured with fMRI) may provide divergent information. Nevertheless, the continuous presence of the fMRI signal and its correlations during sleep supports the existence of brain activity that does not require attention, alertness, or voluntary mentation.

Studies that have more specifically examined the effect of sleep depth (judged from EEG features such as the level of theta activity (4–8Hz) or slow-wave activity (SWA) (< 4.5Hz)) found a preservation of corticocortical connectivity during light sleep (Horovitz et al., 2008; Larson-Prior et al., 2009; Spoormaker et al., 2010) but a decrease in such connectivity during deep sleep (Horovitz et al., 2009; Larson-Prior et al., 2011; Samann et al., 2011; Spoormaker et al., 2011; Spoormaker et al., 2012; Wu et al., 2012), an observation that is consistent with EEG studies of connectivity and cortical excitability (Boly et al., 2012a; De Gennaro et al., 2001; Massimini et al., 2010). In particular, neuroimaging studies have reported reductions in corticocortical connectivity with sleep in fronto-parietal networks (Braun et al., 1997; Hofle et al., 1997; Horovitz et al., 2009; Kaufmann et al., 2006; Larson-Prior et al., 2011; Samann et al., 2011; Spoormaker et al., 2012). The results from PET studies indicate that these networks exhibit a reduction in CBF (Braun et al., 1997; Hofle et al., 1997), thus they may support waking functions such as attention, memory, and consciousness (see following sections). An interesting, but poorly understood, finding in this regard has been a decrease in the anti-correlation during light sleep between the default mode network (DMN) on one hand and the attention (DAN) and executive control (ECN) networks on the other (Larson-Prior et al., 2011; Samann et al., 2011).

During REM sleep, PET has shown rCBF increases in brainstem, thalamus, and extra-striate occipital cortex, an observation that is consistent with a network that supports the PGO waves that are characteristic of this sleep stage (Braun et al., 1998). In addition, rCBF increases have been observed in hippocampal and amygdalar regions. These increases may play a role in memory consolidation and/or emotion regulation (Braun et al., 1998; Hong et al., 2009). The few fMRI studies that have been performed so far have been largely consistent with this. Specifically, fMRI studies have shown a correlation between level and onset of REM with signal in the thalamus, occipital cortex, and pons (Miyauchi et al., 2009; Wehrle et al., 2005). Exploiting the superior temporal resolution of fMRI relative to PET, instances of rapid eye movements were found to correlate with signal in the amygdala, hippocampus, cingulate, and sensory cortices; this is consistent with the PET results and further points to their possible involvement in memory consolidation (Wehrle et al., 2007).

Sleep-specific changes in fMRI activity have also been studied by correlating it with sleep-specific EEG features. In fact, most EEG patterns used to define sleep stage (e.g., power in alpha, delta, and sub-delta bands, K-complexes, spindles, see Table) have been studied in combination with fMRI (Andrade et al., 2011; Bergmann et al., 2012; Dang-Vu et al., 2005; Hofle et al., 1997; Jahnke et al., 2012; Larson-Prior et al., 2011; Laufs, 2008; Laufs et al., 2006; Olbrich et al., 2009; Picchioni et al., 2011; Picchioni et al., 2009; Schabus et al., 2007; Schabus et al., 2012) and, prior to that, with PET (e.g. (Dang-Vu et al., 2005; Hofle et al., 1997).

Quiet waking is characterized by alpha activity. An increase in alpha activity has been interpreted as a disconnection from the external world (Hobson and Pace-Schott, 2002) and correlates with nodes of the DMN (Larson-Prior et al., 2011). Decreases in alpha could indicate falling asleep (N1), when accompanied by an increase in theta activity, or becoming more alert and engaged with the external world, when accompanied by faster EEG activity (beta and gamma) (see Table). In the descent to sleep, the correlation between alpha activity and the DAN decreases (Larson-Prior et al., 2011). Over longer time periods, alpha activity



also correlates with the anterior insula; this could be related to the subject trying to avoid falling asleep and remain awake, or it could be a reflection of intermittent transitions between wake and N1 (Larson-Prior et al., 2011).

The EEG landmarks of N2 are spindles and K-complexes (Table). PET studies show that spindle incidence negatively correlates with thalamic CBF (Dang-Vu et al., 2010; Hofle et al., 1997). fMRI studies provide better temporal discrimination and detect two networks: one involving paralimbic structures (anterior cingulate cortex and insula) and neocortical areas (superior temporal gyrus) and another involving motor networks (Schabus et al., 2007). K-complexes correlate with BOLD signal levels in thalamus, brainstem, and sensorimotor areas and anti-correlate with signal in anterior insula (Jahnke et al., 2012). These two networks are thought to support the dual function of K-complexes in the promotion of sleep and arousal (Colrain, 2005).

N3 is characterized by increased SWA. PET studies show a global decrease in rCBF with increase in SWA (Dang-Vu et al., 2005; Dang-Vu et al., 2008; Hofle et al., 1997). This is consistent with the findings from the comparison of sleep stages reported above. It has been suggested (Dang-Vu et al., 2010) that these changes may be driven by the intermittent neuronal hyperpolarizations characteristic of the so called “down” portion of the “up-down” state cycling that is characteristic of N3 (Steriade and Timofeev, 2003). The better temporal discrimination of fMRI, this phasic activity produced increases in the BOLD signal in a variety of areas, including medial frontal gyrus, parahippocampal gyrus, precuneus, posterior cingulate cortex (PCC), ponto-mesencephalic tegmentum, and cerebellum (Dang-Vu et al., 2008). The correlated activity in the pons includes nucleus coeruleus, an area originally associated with wake but seen active in synchrony with slow waves in animal models (Steriade, 2005). It should be noted that these phasic changes occur against a background of reduced baseline activity in N3 compared to wakefulness and therefore may be of a different nature than phasic changes that occur during wakefulness.

## SLEEP AND MEMORY

### Role of hippocampus in memory consolidation

It is becoming clear that the role of sleep in memory consolidation goes beyond a passive role of protecting the brain from interference (Ellenbogen et al., 2006). A prominent theory of sleep dependent-learning is centered on the idea of a reversal of the neocortico-hippocampal dialogue (see Figure) during N3 (Buzsaki, 1998; Hasselmo, 1999). During N3, acetylcholine levels decrease throughout the brain (Marrosu et al., 1995); this leads to a disinhibition of the hippocampus (Hasselmo, 1999). This disinhibition is reflected in the appearance of fast spike-ripple complexes (Battaglia et al., 2004; Isomura et al., 2006; Molle et al., 2006; Sirota et al., 2003), which are a neuro-electrical hippocampal feature that may trigger neocortical plasticity as part of a reversal of information exchange.

Early neuroimaging evidence for this hippocampal involvement in memory consolidation came from a landmark PET study, which demonstrated an increase in hippocampal CBF during N3 and correlated that activity with the overnight improvement on a spatial navigation task (Peigneux et al., 2004). This study began to fill a critical gap in the literature because, compared to earlier EEG studies, the increased spatial resolution allowed the investigators to make specific predictions about the relationship between sleep-dependent performance improvements on a particular memory task and sleep-specific activity in a particular brain region on which that task is known to depend. Despite the importance of this finding, it should be realized that it cannot be generalized to other types of memory and that the benefits of sleep for memory are not limited to N3.

If a reversal of the neocortico-hippocampal dialogue during sleep underlies memory consolidation and if the hippocampus is indeed disinhibited during this process, one might expect an increase in neocortico-hippocampal functional connectivity during sleep. To test this hypothesis, Andrade and colleagues (Andrade et al., 2011) performed a functional connectivity analysis with the hippocampal formation as the seed region. Interestingly, they found that while neocortico-hippocampal functional connectivity increased during N2 (compared to wakefulness), it decreased in N3. The authors rationalize these findings by stating that information exchange may occur in N2, whereas an isolated neocortex during N3 may allow segregated processing of the information. However, the levels of acetylcholine are lowest during N3, and this would lead to the prediction of a greater disinhibition of the hippocampus; therefore hippocampal-cortical connectivity should be highest in N3.

### **Sleep-specific EEG features and memory**

Sleep is characterized by a variety of EEG features that may have relevance to memory consolidation, and a number of studies have investigated the fMRI correlates of these features (Table). Spindles are generated when nonspecific thalamocortical neurons are hyperpolarized by GABAergic neurons in the thalamic reticular nucleus and change their firing pattern from tonic to phasic (Steriade et al., 1985). Steriade (Steriade, 2005) proposed that spindles may engender synaptic plasticity by potentiating neocortical neurons in a way that can be considered similar to the tetanus in long-term potentiation studies, and the results from several studies indicate that spindles indeed play a role in sleep-dependent memory consolidation (reviewed by (Nader and Smith, 2003)).

Schabus and colleagues (Schabus et al., 2007) were the first to measure the neural correlates of spindles using fMRI. Fast spindles were correlated with increased activity in the hippocampus. This result was only present when contrasting the activity of fast spindles (13.1 – 14.9 Hz) with that of slow spindles (11.1 – 12.9 Hz); significant hippocampal activity was not present when examining the activity of fast spindles alone. The authors, therefore, were limited to discussing the relative functional significance of fast versus slow spindles. The study by Andrade and colleagues (Andrade et al., 2011) discussed above also examined the interaction between hippocampal functional connectivity and the presence or absence of a spindle using moderated multiple regression, which is also known as a psychophysiological interaction analysis. If spindles indeed engender synaptic plasticity in the neocortex, then neocortico-hippocampal functional connectivity should increase in the presence of a spindle compared to in the absence of a spindle. This hypothesis was supported.

A number of studies have also investigated the fMRI correlate of SWA, which have been subdivided into delta oscillations, slow oscillations, and infraslow oscillations (see Table) (Vanhatalo et al., 2004). Activity in each of these bands is thought to originate from unique neuro-physiological origins and each one may represent a unique aspect of sleep. In a parametric design that generated volume-by-volume EEG-fMRI correlations, these three bands were correlated with fMRI activity across all sleep stages (Picchioni et al., 2011). Infraslow oscillations were positively correlated with activity in the hippocampus and parahippocampal gyri, and these correlations were unique to infraslow oscillations. Therefore, infraslow oscillations may also organize the coordinated, reciprocal activity between the hippocampus and neocortex (Balduzzi et al., 2008).

### **Role of REM for memory**

PGO waves are correlated waves of electrical activity that propagate from the pons to the lateral geniculate nucleus to the occipital lobe and have only been observed during REM

(Sakai, 1985). The neurons in the pons that initiate PGO waves project to several regions including the hippocampus (Datta et al., 1998). In animals, PGO waves correlate with sleep-dependent memory improvements (Datta, 2000), and actively manipulating them augments the improvements, an observation that establishes a causal relationship (Mavanji and Datta, 2003). The rapid eye movements of REM sleep have been correlated with the individual activity in the pons, thalamus, and primary visual cortex in humans using PET (Peigneux et al., 2001) and fMRI (Miyauchi et al., 2009; Wehrle et al., 2005), but there are no sleep PET or sleep fMRI studies that examined whether PGO waves in humans correlate with memory improvement (Dang-Vu, 2012).

### **fMRI correlates of sleep-dependent memory improvements**

Although there is ample evidence for the beneficial effects of sleep for a variety of memory functions, there are relatively few examples of studies that have combined sleep fMRI with an explicit measure of memory before and after sleep. Using a retinotopically specific texture discrimination task, Yotsumoto and coworkers (Yotsumoto et al., 2009) found increased fMRI activity in the trained primary visual cortex hemisphere during sleep, and this increase correlated with the performance improvement after sleep. Using a face/scene version of the paired associate word list memory task, Bergmann and colleagues (Bergmann et al., 2012) tested specific predictions about activity in the fusiform face area and parahippocampal place area. In another study, van Dongen, and colleagues (van Dongen et al., 2011) used a memory task that is very similar to the paired associate face/scene task described above, and the focus of this study was also on the fusiform face area. It was discovered that neocortico-fusiform face area functional connectivity increased during light sleep. At the group level, connectivity in the medial prefrontal cortex (MPFC) correlated positively with performance. In the most direct sense, the results from this study provide the first piece of evidence that connectivity during sleep plays an important role in sleep-dependent memory consolidation.

### **fMRI during reactivation of memories in sleep**

Experimentally manipulating the natural electrical and chemical changes that characterize sleep can affect its benefit on memory (Arizpe et al., 2012; Gais and Born, 2004; Marshall et al., 2006; Mavanji and Datta, 2003). Inspired by this notion, a number of studies have attempted to selectively reactivate memories during sleep. Exposing subjects to a unique odor during encoding and during subsequent sleep facilitates retrieval on a hippocampus-dependent declarative memory task, and this procedure resulted in an increase in hippocampal activity during sleep compared to periods without odor presentation (Rasch et al., 2007). In addition, this procedure does not increase hippocampal activity when administered during wakefulness (Diekelmann et al., 2011). van Dongen and colleagues (van Dongen et al., 2012) took this paradigm one step further by examining parahippocampal connectivity during sleep. The stimuli that were delivered were sounds instead of odors. Increased parahippocampal connectivity was observed in primary visual cortices and visual association cortices. At the group level, connectivity in the precuneus correlated positively with behavioral index of performance. It is at least clear from this study that individual differences in connectivity may be important to the process where a tagged memory is preferentially strengthened during sleep.

## **SLEEP AND AROUSAL**

### **The multifaceted nature of arousal**

The concept of arousal is exceedingly complicated and can be approached from several unique directions. Arousal can be considered in terms of the seminal work by Moruzzi and Magoun (Moruzzi and Magoun, 1949) on the ARAS in the midbrain-pontine reticular



formation. Arousal can also be considered in terms of thalamocortical connectivity. As discussed above, the thalamus contains nonspecific nuclei and these nuclei can act as a gatekeeper where sensory signals are blocked from being transmitted to the neocortex. Arousal can also be considered in terms of responsiveness to stimuli during sleep and the associated neural changes. Studies in this area are often labeled as sensory or environmental awareness studies or arousal threshold studies. This is very important because a reduced behavioral response to sensory stimuli is one of the fundamental definitions of sleep that is used across the phylogenetic spectrum. Arousal can be considered in terms of cortical arousal or cortical activation. Finally, arousal can be discussed in terms of the unique cortical arousal that is present in REM. For example, in the absence of external sensory stimulation during REM, how does the thalamocortical system generate arousal internally?

### **K-complexes, sleep spindles, and arousal**

An important EEG feature with relevance to arousal is the K-complex (Halasz et al., 1985). K-complexes are < 2.0 Hz-waveforms with a sharp initial negative component followed by a slower positive component (Rechtschaffen and Kales, 1968). Similar to slow waves (Finelli et al., 2001), K-complexes are maximal over the frontocentral region of the scalp (Niiyama et al., 1995; Paiva and Rosa, 1991). K-complexes are unique because they occur spontaneously and can also be evoked. There is considerable controversy regarding whether K-complexes are arousal-enhancing or sleep-enhancing (Colrain, 2005; Halasz, 1993; Halasz et al., 2004). On one hand, K-complexes are more likely to be evoked in response to the presentation of a personally meaningful stimulus (Voss and Harsh, 1998). On the other hand, there is a progressive increase in K-complex density during the periods prior to the onset of stage N3 (De Gennaro et al., 2000). Jahnke and colleagues (Jahnke et al., 2012) analyzed the fMRI correlates of spontaneous K-complexes with a two-step approach. First, they performed an event-related fMRI analysis where the onset of each spontaneous K-complex served as the onset of the predicted hemodynamic response. Second, they used the significant clusters from this analysis as variables in a series of dynamic causal models. This allowed the investigators to test the fit of a series of hypothesized causes among the areas of activity during a K-complex. For example, the model with a K-complex causing activity in the auditory cortex was the model with the best fit.

A common technique in EEG research is the acoustic oddball paradigm. Investigators utilizing this paradigm present, for example, one 1500 Hz tone for every four 1000 Hz tones. The EEG response to the "deviant" tone is typically larger than the response to the other tones. This paradigm has been applied to sleep studies by ensuring all stimuli are sub-arousal threshold. Czisch and colleagues (Czisch et al., 2009) applied this paradigm to an event-related fMRI study during sleep where the onset of each deviant tone served as the onset of the predicted hemodynamic response. When examining activity associated with the presence of a deviant tone that also elicited a K-complex, there was activity in the auditory cortex. This was interpreted as supporting the idea that evoked K-complexes serve to monitor the environment.

Sleep spindles are also highly relevant to discuss in the context of arousal because, among other reasons, the first substantial increase in arousal threshold occurs immediately after the first sleep spindle (Bonnet and Moore, 1982). Other stimulation studies delivered constant stimuli at a constant rate during sleep fMRI and classified the stimuli according to whether they were coincident with a spindle by chance (Dang-Vu et al., 2011). Although increased activity was observed in the auditory cortex during wakefulness, this increase was absent when the tone was delivered during a spindle. Similar results were obtained when the stimuli were delivered during the negative-going phase of the slow oscillation (Schabus et al., 2012). The authors discussed these results in terms of the idea that the thalamus no longer relays sensory information to the cortex during a spindle. These results point to a promising

research avenue, and suggest the importance of further study into thalamocortical connectivity. It could be predicted that thalamocortical connectivity would decrease during sleep.

### REM sleep

PGO waves have been implicated in the cortical activation and dream imagery that accompanies REM. This idea is one of the cornerstones of the Activation-Synthesis Hypothesis (Hobson and McCarley, 1977) and its more recent incarnation, the Activation-Input Source-Neuromodulation model (Hobson et al., 2000). According to this model, the brain interprets PGO waves as if they were external signals. In a methodologically thorough study, Miyauchi and colleagues (Miyauchi et al., 2009) compared the brain activity associated with waking saccades in total darkness to the brain activity associated with rapid eye movements in REM sleep using event-related fMRI. Although previous reports did not include the primary visual cortex as a region that increased its activity during REM (Braun et al., 1998), the results of the present study did find such activity. In addition, primary visual cortex activity was not observed to be linked with waking saccades in total darkness. Most important, the authors showed that the timing of the BOLD response in the pons, thalamus, and primary visual cortex follows a sequential pattern, an observation that suggests the existence of a PGO-wave-like phenomenon that preceded each eye movement.

Thalamocortical connectivity is an important concept for understanding REM and the associated cortical arousal/activation. Thalamocortical functional connectivity has been measured in REM. Wehrle and colleagues (Wehrle et al., 2007) delivered sub-arousal threshold acoustic stimuli during both tonic REM (without eye movements) and phasic REM (with eye movements); however, for the connectivity analysis, a nuisance regressor was used to control for the effects of acoustic stimulation. Thalamocortical connectivity was higher in phasic REM compared to tonic REM. In addition, signal in the thalamus correlated with signal in sub-cortical brain regions in the limbic system. These results are exciting because they suggest the brain operates by means of a "closed internal loop" during REM, and this is consistent with the idea that cortical arousal/activation is generated internally during REM.

## SLEEP AND CONSCIOUSNESS

Consciousness can be thought of as having a level and a content, a viewpoint which can be paralleled with the distinct concepts of arousal and awareness (Laureys, 2005; Zeman, 2001). Both decrease during the progressive stages of non-REM sleep and may be even further reduced in disorders of consciousness such as coma (Laureys, 2005; Zeman, 2001). Arousal level (i.e., wakefulness) and awareness increase or decrease together with few exceptions. During REM the content of consciousness (awareness) is high but the level of consciousness (arousal level) is low. Patients in a vegetative state can be awake and can have their eyes open but their content of consciousness is low (Laureys, 2005).

The natural variations in awareness and arousal that occur during sleep have been studied to investigate the major networks that support these processes (see review by (Heine et al., 2012)). In the following subsections, we will first describe these networks and then describe how they change during sleep.

### Networks associated with consciousness

Awareness can be divided into awareness of the self and awareness of the environment (Boly et al., 2008; Laureys, 2005). Self-awareness (Gusnard et al., 2001) and conscious self-representation (Lou et al., 2004) are thought to be supported by the DMN, a set of brain areas which, at rest, have a relatively high rCBF (Gusnard et al., 2001; Raichle et al., 2001)

and a high level of correlated BOLD signal fluctuations (Greicius et al., 2003). This network includes the PCC/precuneus, the MPFC, and the left and right inferior parietal cortices (Raichle et al., 2001) (see Figure). Its nodes are among the most connected brain areas, both anatomically (Hagmann et al., 2008) and functionally (Buckner et al., 2009).

Awareness of the environment is thought to be supported by the DAN (Corbetta et al., 2000; Shulman et al., 1999). This bilateral fronto-parietal network includes superior parietal lobule and frontal eye fields. Other attention-related networks that are relevant to awareness of the environment are those thought to control information processing (Vincent et al., 2008). They comprise the ECN, including dorsolateral prefrontal cortex and intra-parietal sulcus, the salience network, consisting of the anterior insula and the orbitofrontal cortex, and the cingulo-opercular network including anterior cingulate and frontal operculum (Dosenbach et al., 2006; Seeley et al., 2007). In many fMRI connectivity studies, the DAN and ECN are jointly referred as the anticorrelated network (ACN).

### Consciousness and the descent to sleep

fMRI connectivity between nodes of the DMN is strong at rest. In the transition to sleep no significant changes (Horovitz et al., 2008; Larson-Prior et al., 2009), or small decreases in DMN connectivity (Samann et al., 2011) have been reported. The differences could be related to study power, or whether subjects reached earlier or late N1 (Picchioni et al., 2008). Resting data from sleep-deprived subjects show decreased DMN connectivity (De Havas et al., 2012; Samann et al., 2010), which could be intrinsic to the sleep deprivation or a reflection of changes in vigilance. Network stability during the transition to sleep has implications beyond sleep studies, since most resting state fMRI studies lack control of the vigilance state.

PCC-MPFC connectivity was found to decrease during N2 (Samann et al., 2011; Wu et al., 2012). This reduction is consistent with the notion that PCC-MPFC connectivity reflects self-awareness (Vogt and Laureys, 2005), which is known to be greatly reduced with the deepening of sleep beyond N1 (Hobson and Pace-Schott, 2002). The connectivity between the DMN and its anticorrelated network decreases at sleep onset (Samann et al., 2011).

During N3, PCC and MPFC are further decoupled without much change in the correlations within each node. Interestingly, connectivity between parietal DMN nodes was found to strengthen during this stage (Horovitz et al., 2009; Samann et al., 2011; Spoormaker et al., 2010; Wu et al., 2012) (although one study reports no changes in DMN connectivity with sleep (Koike et al., 2011)). Also during N3, the connectivity between nodes of the ECN decreased compared to wakefulness (Samann et al., 2011). These findings further support the notion that the connectivity between frontal and parietal nodes in DAN, DMN, and ECN reflects consciousness.

The findings of DMN connectivity during REM sleep have so far been inconclusive. Both increased (Wu et al., 2012), and decreased (Koike et al., 2011) connectivity between DMN nodes has been found; additional studies will be needed to clarify this.

### Network interactions in the descent to sleep

During wakefulness, DMN anti-correlates with DAN and ECN (Fox et al., 2005; Larson-Prior et al., 2011; Samann et al., 2011). Such anti-correlations were found to decrease during sleep (Larson-Prior et al., 2011; Samann et al., 2011). Hierarchical clustering analysis shows that the frontal-parietal networks are integrated during wakefulness but decoupled during non-REM sleep (Larson-Prior et al., 2011; Spoormaker et al., 2011). These findings invite speculation that DMN-DAN interactions may reflect the level of consciousness that is

required for information integration (Boly et al., 2012b; Heine et al., 2012; Larson-Prior et al., 2011; Spoormaker et al., 2010; Tononi and Cirelli, 2006).

### Arousal from a consciousness perspective

Electrophysiological studies show a decrease in thalamocortical and corticocortical connectivity during NREM sleep (Steriade, 2001) and during the vegetative state (Laureys et al., 1999); in both cases this connectivity is restored when consciousness is restored. PET studies show a decrease in thalamic activity during N1 (Kaufmann et al., 2006) and N3 (Braun et al., 1997) compared to wakefulness. The thalamic rCBF is restored immediately upon awakening (Balkin et al., 2002), when consciousness is restored but alertness is not. Thalamic rCBF is also high during REM (Braun et al., 1997), when the content of consciousness is elevated compared to N3. These and other studies (see reviews by (Franks, 2008; Noirhomme et al., 2010)) suggest that cortical arousal is sustained through the thalamus, and that consciousness requires thalamocortical connectivity in addition to corticocortical connectivity (Figure). This is true for the pathological loss of consciousness in coma as well as the loss of awareness under anesthesia. It is important to mention that natural sleep fulfills a unique set of functions that are not fulfilled during these other alterations in consciousness. However, there still may be lessons to learn by comparing them. They share many phenomenological, electrophysiological, and behavioral characteristics (Alkire et al., 2008), and a better understanding of the subtle distinctions between them may lead to a more refined way to alter consciousness during clinical interventions (Brown et al., 2010).

Seed region analysis (Picchioni et al.) and hierarchical clustering analysis indicates that the thalamus as a whole is highly connected to the cortex during wakefulness but is isolated during non-REM sleep (Spoormaker et al., 2012). This is in line with the notion that the thalamus is a co-modulator of the corticocortical connectivity in support of consciousness (Boly et al., 2012a).

## SUMMARY AND OUTLOOK

Sleep and the functional connectome are research areas with considerable overlap. Neuroimaging studies of sleep based on EEG-PET and EEG-fMRI are revealing the brain networks that support sleep, as well networks that may support the roles and processes attributed to sleep. For example, phenomena such as arousal and consciousness are substantially modulated during sleep, and one would expect this modulation to be reflected in altered network activity. Thus, characterizing brain activity changes across the sleep-wake cycle may provide a fruitful basis for the mapping of networks underlying these phenomena. It should be realized, however, that the neuromodulatory changes during sleep may not only alter network configurations but also may change the level and location of network input. This complicates the interpretation of fMRI correlations in terms of connectivity in cortical networks.

A number of recent studies have started to explore the presence of transient network activity underlying spontaneous fMRI signal fluctuations (Liu and Duyn, 2013; Smith et al., 2012; Tagliazucchi et al., 2013) based on the notion that much of the brain's activity may not obey the stationarity of network properties assumed by conventional analysis method such as independent component analysis and seed-based correlation. Such novel analysis approaches may be particularly useful for the study of sleep, when many transient brain interactions occur (e.g., those related to EEG features such as K-complexes, spindles, and slow waves). A particular example is the intriguing possibility of studying the hippocampal-cortical interactions that have been suggested to underlie memory consolidation, which is one of the functions attributed to sleep. In this and other networks, the study of transient network

activity based on fMRI data alone may provide information complementary to that obtained from correlating EEG features with fMRI signals (Liu and Duyn, 2013).

This review has discussed several examples in which roles attributed to sleep are reflected in network connectivity. It should be realized that some of these roles are not exclusively supported by sleep. For example, some evidence exists that memory consolidation, can occur during quiet waking or rest (Carr et al., 2011). In addition, there is some preliminary evidence that neocortico-hippocampal connectivity during resting-state fMRI has relevance to subsequent memory retrieval (Tambini et al., 2010). This is an intriguing area that is still relatively unexplored.

It is also important to consider that it is difficult to draw causal conclusions from many of these connectivity studies because of their reliance on correlational measures. Improving the research in this area would necessitate the use of more sophisticated statistical techniques such as dynamic causal modeling and effective connectivity analysis (for review see (Duyn, 2012)).

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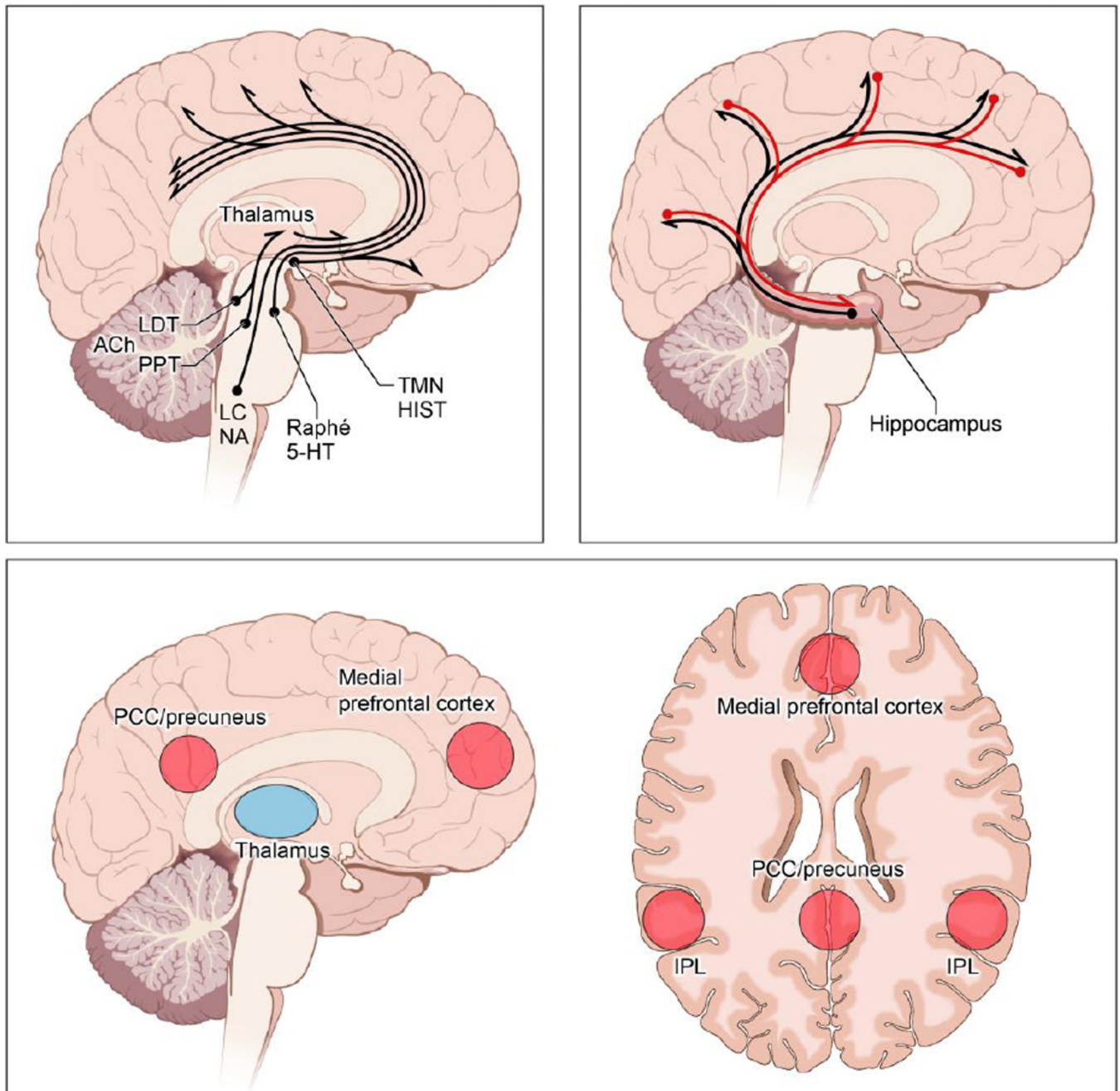


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**Highlights**

- Sleep has a number of adaptive functions that support waking activity
- EEG-fMRI studies reveal brain networks that support sleep
- Arousal and consciousness modulations by sleep are reflected in network connectivity
- fMRI during sleep allows the study of the hippocampal role in memory consolidation

**Figure.**

Networks that undergo changes during sleep

Top left (A): arousal network

Arousal modulations during sleep are under the control of the ascending reticular activating system (ARAS) and its projections. Modulatory control is effectuated by a variety of neurotransmitters (see section “brain circuits that support sleep”).

Top right (B): memory network

A model for hippocampal-cortical connections associated with memory storage and consolidation. During wakefulness, the dominant information flow is from neocortex to

hippocampus (red lines). During N3, there is a putative reversal of this information flow (black lines), which is effectuated by modulatory cholinergic influences.

Bottom (C): consciousness network

During wakefulness, substantial connectivity is observed between DMN nodes (red) and between thalamus (blue) and cortex. During N3, the frontal node of the DMN reduces its connectivity with the rest of the network. In addition, thalamocortical connectivity is reduced.

HIST = histamine; 5-HT = serotonin; NA = noradrenaline; ACh = acetylcholine.

IPL:inferior parietal lobule



Sleep nomenclature and rhythms

Top panel indicate the different names used to classify sleep stage.

Bottom panel: Each column highlights the hallmarks of each sleep stage.

Table 1

Alert wake	Quiet wake	N1	N2	N3	R	I
		Stage1	Stage 2	Stages 3&4	REM	2
		Light sleep		SWS		3
beta	alpha	theta	K-complex	SWA	theta	
(15–20Hz)	(8–12Hz)	(4–8Hz)	(single event)	(<4.5Hz)	(4–8Hz)	
gamma			Spindles	infralow		
(>20 Hz)			(11–15Hz)	(<0.1)	saw-tooth waves	
			0.5 s duration	slow oscillation	Eye movement	
high EMG				(<1Hz)	low EMG	
				delta	PGO waves	
				(1–4Hz)		

<sup>1</sup> Sleep classification according to AASM, 2007. AASM Manual for the scoring of Sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine, Westchester, IL.

<sup>2</sup> Sleep classification according to Rechtschaffen, A., Kales, A., 1968. A manual of standardized terminology, techniques and scoring system for sleep stage of human subjects. U.S. Department of Health, Education and Welfare. Public Health Service. National Institutes of Health, NINDS, Bethesda, MD.

<sup>3</sup> Commonly used names to indicate sleep stages

Abbreviation: EMG: electromyography; SWA: slow wave activity; SWS: slow wave sleep; PGO: ponto-geniculo-occipital